

	Type	L #	Hits	Search Text	DBs	Time Stamp	Comments	Error Definition
1	BRS	L2	2	1 same amide	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/03/28 07:43		0
2	BRS	L1	13	cyclis3 same conotoxin	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/03/28 07:53		0
3	BRS	L3	29099 95	MVIA or GVIA or SVIB or SVIA or TVIA or MVIC or GVIA or GVIB or PVIA or GS or GI or IMI or PNIA or PNAB or SII or MII or GIIA or GIIB or GIIC or PIIA	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/03/28 07:57		0
4	BRS	L4	6	1 same 3	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/03/28 07:57		0
5	BRS	L5	2118	peptide adj linker	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/03/28 07:57		0
6	BRS	L6	1	1 same 5	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/03/28 07:58		0
7	BRS	L7	0	(prepar\$5 or synthesis\$2) same 1	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/03/28 08:00		0
8	BRS	L9	0	craik adj david adj james.in.	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/03/28 08:00		0
9	BRS	L10	0	david adj james adj craik.in.	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/03/28 08:01		0
10	BRS	L11	0	daly adj norelle.in.	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/03/28 08:01		0
11	BRS	L12	0	daly adj norelle adj lee.in.	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/03/28 08:01		0
12	BRS	L13	1	nielsen adj katherine.in.	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/03/28 08:02		0
13	BRS	L8	1	craik adj david.in.	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/03/28 08:05		0
14	BRS	L14	0	craik adj james adj david.in.	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/03/28 08:04		0

	Type	L #	Hits	Search Text	DBs	Time Stamp	Comments	Error Definition	Error
15	BRS	L16	4	craik adj d adj j.in.	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/03/28 08:06			0

FILE 'HOME' ENTERED AT 08:11:08 ON 28 MAR 2003

=> file medline caplus biosis embase scisearch agricola  
COST IN U.S. DOLLARS

	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	0.21	0.21

FILE 'MEDLINE' ENTERED AT 08:11:38 ON 28 MAR 2003

FILE 'CAPLUS' ENTERED AT 08:11:38 ON 28 MAR 2003  
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=> s cycli? conotoxin  
L1 1 CYCLI? CONOTOXIN

=> d l1 1 ibib abs

L1 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2003 ACS  
ACCESSION NUMBER: 2000:191100 CAPLUS  
DOCUMENT NUMBER: 132:237373  
TITLE: Preparation of \*\*\*cyclized\*\*\* \*\*\*conotoxin\*\*\*  
peptides  
INVENTOR(S): Craik, David James; Daly, Norelle Lee; Nielsen,  
Katherine Justine  
PATENT ASSIGNEE(S): University of Queensland, Australia  
SOURCE: PCT Int. Appl., 43 pp.  
CODEN: PIXXD2  
DOCUMENT TYPE: Patent  
LANGUAGE: English  
FAMILY ACC. NUM. COUNT: 1  
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000015654	A1	20000323	WO 1999-AU769	19990914
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 9960705	A1	20000403	AU 1999-60705	19990914
AU 747006	B2	20020509		
EP 1129106	A1	20010905	EP 1999-947111	19990914
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				

PRIORITY APPLN. INFO.: AU 1998-5895 A 19980914  
WO 1999-AU769 W 19990914

AB \*\*\*Cyclized\*\*\* \*\*\*conotoxin\*\*\* peptides were prepd. for the  
therapeutic treatment of mammals. Thus, cyclo[CKGKGAKCSRLMYDCCTGSCRSKGKCTR  
NGLPG], a cyclic analog of MVIIA having the linking moiety TRNGLPG, was  
prepd. by the solid-phase method.

REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS

=> s conotoxin  
L2 14277 CONOTOXIN

=> s 12 (p) cycli?  
5 FILES SEARCHED...  
L3 333 L2 (P) CYCLI?

=> s 13 (p) amide  
L4 2 L3 (P) AMIDE

=> duplicate remove l4  
DUPLICATE PREFERENCE IS 'CAPLUS, SCISEARCH'  
KEEP DUPLICATES FROM MORE THAN ONE FILE? Y/(N):n  
PROCESSING COMPLETED FOR L4  
L5 1 DUPLICATE REMOVE L4 (1 DUPLICATE REMOVED)

=> s 15 not l1  
L6 1 L5 NOT L1

=> d 16 1 ibib abs

L6 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1994:31193 CAPLUS

DOCUMENT NUMBER: 120:31193

TITLE: Synthesis of .alpha.-conotoxin SI, a bicyclic  
tridecapeptide amide with two disulfide bridges:  
illustration of novel protection schemes and oxidation  
strategies

AUTHOR(S): Munson, Mark C.; Barany, George

CORPORATE SOURCE: Dep. Chem., Univ. Minnesota, Minneapolis, MN, 55455,  
USA

SOURCE: Journal of the American Chemical Society (1993),  
115(22), 10203-10  
CODEN: JACSAT; ISSN: 0002-7863

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Several routes are described and compared for the synthesis of .alpha.-  
\*\*\*conotoxin\*\*\* SI, a tridecapeptide \*\*\*amide\*\*\* of sequence  
H-Ile-Cys2-Cys3-Asn-Pro-Ala-Cys7-Gly-Pro-Lys-Tyr-Ser-Cys13-NH2, with  
bicyclic disulfides connecting Cys2 with Cys7, and Cys3 with Cys13. The  
linear sequence was assembled smoothly on tris(alkoxy)benzylamide (PAL)  
supports, using stepwise 9-fluorenylmethoxycarbonyl (Fmoc) solid-phase  
chem. Side-chain protection of Cys was provided by S-2,4,6-  
trimethoxybenzyl (Tmob) at four positions or by suitable pairwise  
combinations of S-Tmob and S-acetamidomethyl (Acm). Acidic  
cleavage/deprotection of these peptide resins with trifluoroacetic acid  
(TFA)-CH2Cl2-Et3SiH-H2O-anisole (95:4:0.5:0.5:0.5), at 25.degree. for 2 h  
gave the corresponding peptide \*\*\*amides\*\*\* in high yields (90-97%);  
those Cys residues originally blocked by S-Tmob were converted to the free  
sulfhydryls, whereas Cys(Acm) residues remained blocked. The fully  
deprotected linear tetrasulfhydryl \*\*\*conotoxin\*\*\* was oxidized  
successfully in dil. pH 7.5 soln. in the presence of 1% (vol./vol.) DMSO  
at 25.degree. for 7 h, providing monomeric bicyclic peptide in an overall  
yield of 39%. Other simultaneous procedures gave poor yields and/or  
extensive oligomers and polymers, in part due to soly. problems. Further  
soln. synthesis strategies relied on sequential disulfide pairing as  
dictated by the original protection scheme. A monocyclic, bis(Acm)  
intermediate, with the smaller loop (Cys2 with Cys7) already closed by the  
soln. DMSO oxidn. procedure, was \*\*\*cyclized\*\*\* further with  
Tl(O2CCF3)3 (1.2 equiv) in TFA-anisole (19:1) at 4.degree. for 18 h. The  
resp. oxidn. yields were 62 and 65%, and the final overall yield of  
monomeric \*\*\*conotoxin\*\*\* reflecting cleavage from the support and the  
two orthogonal oxidn. steps was 38%. Alternatively, the same chem. steps  
and soln. conditions were used to test the strategy of forming the larger  
loop (Cys3 with Cys13) first; individual oxidn. steps each proceeded in  
.apprx.50% yield, and \*\*\*conotoxin\*\*\* was obtained in an overall yield  
of 23%. Simultaneous or orthogonal disulfide bond formation was also  
examd. while the peptide remained anchored to the polymeric support. The  
most promising results started with the appropriate resin-bound precursor,

which was treated with TFA-CH<sub>2</sub>Cl<sub>2</sub>-Et<sub>3</sub>SiH-H<sub>2</sub>O-anisole (7:92:0.5:0.5:0.5), 2 .times. 15 min at 25.degree. remove selectively S-Tmob group from Cys2 and Cys7 without significant loss of chains from the support. The resultant resin-bound dithiol was oxidized with 35 mM CCl<sub>4</sub>-Et<sub>3</sub>N (2 equiv each) in N-methylpyrrolidinone for 4 h at 20.degree. to provide a resin-bound monocyclic bis(Acm) intermediate, which was oxidized further with Tl(O<sub>2</sub>CCF<sub>3</sub>)<sub>3</sub> (2 equiv) in DMF-anisole (19:1) for 18 h at 4.degree.. After acidic cleavage, overall yields of monomeric \*\*\*conotoxin\*\*\* were as high as 14%. Addnl. oligomeric material is apparently incorporated as a network which is retained on the support, accounting for the reduced yields (25-50%, resp. with polystyrene and polyethylene glycol-polystyrene graft supports) obsd. after cleavage of the peptidyl-PAL anchoring linkage. The polymer-supported routes are amenable to further optimization and may offer several advantages over soln. methods.

=> d his

(FILE 'HOME' ENTERED AT 08:11:08 ON 28 MAR 2003)

FILE 'MEDLINE, CAPLUS, BIOSIS, EMBASE, SCISEARCH, AGRICOLA' ENTERED AT 08:11:38 ON 28 MAR 2003

```
L1      1 S CYCLI? CONOTOXIN
L2      14277 S CONOTOXIN
L3      333 S L2 (P) CYCLI?
L4      2 S L3 (P) AMIDE
L5      1 DUPLICATE REMOVE L4 (1 DUPLICATE REMOVED)
L6      1 S L5 NOT L1
```

=> s peptide linker

```
L7      877 PEPTIDE LINKER
```

=> s l3 (p) l7

```
L8      0 L3 (P) L7
```

=> s disulfide

```
L9      198955 DISULFIDE
```

=> s l9 (p) l3

```
L10     26 L9 (P) L3
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=> duplicate remove l10

DUPLICATE PREFERENCE IS 'MEDLINE, CAPLUS, BIOSIS, EMBASE, SCISEARCH'

KEEP DUPLICATES FROM MORE THAN ONE FILE? Y/(N):n

PROCESSING COMPLETED FOR L10

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L11     11 DUPLICATE REMOVE L10 (15 DUPLICATES REMOVED)
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=> s amide link?

```
L12     5040 AMIDE LINK?
```

=> s l3 (p) l12

```
L13     0 L3 (P) L12
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=> d his

(FILE 'HOME' ENTERED AT 08:11:08 ON 28 MAR 2003)

FILE 'MEDLINE, CAPLUS, BIOSIS, EMBASE, SCISEARCH, AGRICOLA' ENTERED AT 08:11:38 ON 28 MAR 2003

```
L1      1 S CYCLI? CONOTOXIN
L2      14277 S CONOTOXIN
L3      333 S L2 (P) CYCLI?
L4      2 S L3 (P) AMIDE
L5      1 DUPLICATE REMOVE L4 (1 DUPLICATE REMOVED)
L6      1 S L5 NOT L1
L7      877 S PEPTIDE LINKER
L8      0 S L3 (P) L7
L9      198955 S DISULFIDE
L10     26 S L9 (P) L3
L11     11 DUPLICATE REMOVE L10 (15 DUPLICATES REMOVED)
L12     5040 S AMIDE LINK?
```

L13

0 S L3 (P) L12

=> log y

COST IN U.S. DOLLARS

SINCE FILE

TOTAL

ENTRY

SESSION

FULL ESTIMATED COST

30.33

30.54

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)

SINCE FILE

TOTAL

ENTRY

SESSION

CA SUBSCRIBER PRICE

-1.30

-1.30

STN INTERNATIONAL LOGOFF AT 08:16:59 ON 28 MAR 2003

=> d his

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FILE 'MEDLINE, CAPLUS, BIOSIS, EMBASE, SCISEARCH, AGRICOLA'  
ENTERED AT

08:11:38 ON 28 MAR 2003

L1 1 S CYCLI? CONOTOXIN  
L2 14277 S CONOTOXIN  
L3 333 S L2 (P) CYCLI?  
L4 2 S L3 (P) AMIDE  
L5 1 DUPLICATE REMOVE L4 (1 DUPLICATE REMOVED)  
L6 1 S L5 NOT L1  
L7 877 S PEPTIDE LINKER  
L8 0 S L3 (P) L7  
L9 198955 S DISULFIDE  
L10 26 S L9 (P) L3  
L11 11 DUPLICATE REMOVE L10 (15 DUPLICATES REMOVED)  
L12 5040 S AMIDE LINK?  
L13 0 S L3 (P) L12

=> log y